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ORIGINAL ARTICLE

A Novel Genes Signature Associated with the Progression of Polycystic Ovary Syndrome

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Abstract

To identify genes involving in the pathogenesis of polycystic ovary syndrome (PCOS). In this study, the comprehensive analysis of GSE8157 was downloaded. Overlapping genes of differentially expressed genes (DEGs) were identified, and enrichment analysis for these genes was performed. A modular network of differentially expressed genes was constructed by weighted gene co-expression network analyses (WGCNA), and a total of 322 differentially expressed genes in 5 stable modules were screened. The correlations of genes of the stable modules in BioGRID 3.4, STRING 10.5, HPRD9 databases were screened, and the interaction network of 104 DEGs was constructed. In addition, some genes and the key words were searched in CTD. A total of 596 differentially expressed genes were screened, including 379 genes that were up-regulated in case group and down-regulated in control group and treat group, and 217 genes that were down-regulated in case group and up-regulated in control group and treat group. The differentially expressed genes were enriched in PPAR signaling pathway, Neuroactive ligand-receptor interaction, cAMP signaling pathway, of which pathways were involved in the cancer development. Finally, 7 important target genes were identified, such as APOC3 was interacted with pioglitazone, ADCY2 involved in cAMP signaling pathway, and the genes (C3AR1, HRH2, GRIA1, MLNR and TAAR2) involved in neuroactive ligand-receptor interaction. In addition, the important target genes were significantly differential expression. These results implied that the 7 important target genes were played an important role in the development and progression of PCOS. Our study implied that genes had played a key role in the development and progression of PCOS, the results showed that microarray can be use as a method for the discovery of new biomarkers and therapeutic targets for PCOS.

Keywords Polycystic ovary syndrome · Microarray · WGCNA · Interaction network analysis

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women. PCOS comprises a broad spectrum of anomalies, including hyperandrogenism, chronic anovulation, obesity, and infertility [1, 2]. PCOS is characterised by anovulation, hyperandrogaenemia and insulin resistance. Hyperinsulinaemia is known to be associated with an increase in cardiovascular risk and the development of diabetes mellitus. Insulin sensitising agents such as metformin are effective in treating features of PCOS, and then they could have wider health benefits than just treating the symptoms of the syndrome [3, 4]. Insulin-sensitising drugs pioglitazone is a thiazolidinedione drug that can improve the metabolic disorder of PCOS patients [2, 5–7]. Many researchers have reported that the insulin-sensitising drugs pioglitazone could improve the metabolic disorder of PCOS patients, while the mechanisms of development and progression of PCOS remain unclear.

Rencently, some microarray analysis occurred to identify the methylation of genes, gene expression and RNA regulation in cervical cancer. Skov et al. analyzed differentially expressed genes in GSE8157, including the gene expression in skeletal muscle of 10 obese women with PCOS treated with

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pioglitazone (30 mg/day for 16 weeks), meanwhile the gene expression changes between these PCOS patients before treatment and 13 healthy women were examined [5]. In this report, pioglitazone therapy restored insulin sensitivity, in part, by a coordinated up-regulation of genes involved in mitochondrial OXPHOS and ribosomal protein biosynthesis in muscle in PCOS, indicating that these transcriptional effects of pioglitazone may contribute to prevent the onset of type 2 diabetes. So it is interesting to further explore the mechanism of PCOS using this method.

In this study, the comprehensive analysis of GSE8157 was performed to identify genes involving in the pathogenesis of PCOS. Overlapping genes of differentially expressed genes (DEGs) in GSE8157 were identified, and enrichment analysis for these genes was performed. In addition, the interaction between genes and genes has been reported to play an important role in the development and progression of PCOS, so the interaction was constructed to further explore the interaction between genes and genes of PCOS. Our study implied that genes had played a key role in the development and progression of PCOS, the results showed that microarray can be use as a method for the discovery of new biomarkers and therapeutic targets for PCOS.

Methods

Data Preprocessing

The data of GSE8157 were downloaded from Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/gds) [8], including 13 control (control group), 10 PCOS patients (case group), and 10 PCOS patients treated with pioglitazone (treat group) [5]. The platform of GSE8157 was GPL570 HG-U133_Plus_2 Affymetrix Human Genome U133 Plus 2.0 Array. In this study, the data of 33 samples were applied to the subsequent analysis. KNN function complements the missing value and the log2 conversion were performed using the impute 1.48.0 package in R language [9, 10]. Then the background correction, quantile normalization and probe summarization were performed by limma 3.36.3 package.

Different Expression Analysis and Function Alanalysis of mRNAs

The normalized data were calculated by eBayes, and genes with FDR (false discovery rate, FDR) < 0.05 and $|\log_2 FC$ (fold change)$| > 1$ were defined as differentially expressed genes (DEGs). Function analysis was performed using GO annotation (http://www.geneontology.org/), and the genes were categorized according to their biological process, molecular function and cellular component [11]. The genes were further assigned to KEGG database (http://www.genome.jp/kegg/pathway.html) [12]. To explore the function of DEGs, functional analysis was performed using the DAVID 6.8 (https://david.ncifcrf.gov) [13]. Significance was expressed as a p value <0.05.

WGCNA and Interaction Analysis

In order to detect cancer development-related genes, a modular network of differentially expressed genes was constructed by weighted gene co-expression network analyses (WGCNA), and the stable modules were screened [14, 15]. The correlations of genes of the stable modules in BioGRID 3.4 (https://thebiogrid.org/), STRING 10.5 (https://string-db.org/), HPRD9 (http://www.hprd.org/) were further screened [16–18]. To investigate the correlations of the differentially expressed genes, the interaction network was constructed using Cytoscape 3.4.0 software (http://www.cytoscape.org). To search for the important genes, the key words (PCOS and pioglitazone), the enriched pathways and the genes that interacted with the drug or that genes in the interaction network were searched in CTD (http://ctdbase.org/) [19].

Results

Analysis of Differentially Expressed Genes

A total of 596 differentially expressed genes were screened, including 379 genes that were up-regulated in case group and down-regulated in control group and treat group, and 217 genes that were down-regulated in case group and up-regulated in control group and treat group. The cluster analysis of these DEGs was performed and the result was shown in Fig. 1 and Additional file.

GO and KEGG Enrichment Analysis of Differentially Expressed Genes

The differentially expressed genes were enriched in biological processes (such as DNA repair, single organismal cell-cell adhesion, oxygen transport, positive regulation of catalytic activity, adenylate cyclase-inhibiting G protein coupled receptor signaling pathway, positive regulation of adenylate cyclase activity, microtubule cytoskeleton organization, membrane depolarization, phosphatidylcholine biosynthetic process, regulation of lipid metabolic process, and visual learning), molecular functions (such as antiporter activity and cholesterol binding), and cellular components (such as integral component of plasma

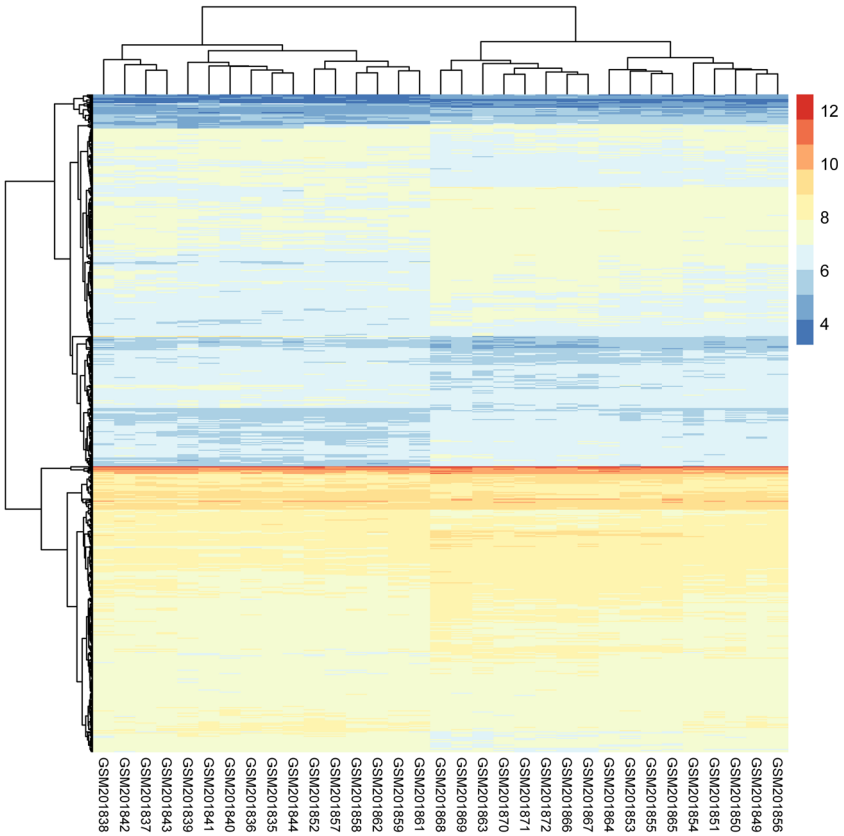

Fig. 1 The cluster analysis of the differentially expressed genes

membrane, perikaryon, and mitochondrial nucleoid) as presented in Table 1. The differentially expressed genes were enriched in PPAR signaling pathway, Neuroactive ligand-receptor interaction, cAMP signaling pathway, of which pathways were involved in the cancer development, as presented in Table 1.

Table 1 GO and KEGG enrichment analysis of differentially expressed genes

Category	Term	PValue
KEGG_PATHWAY	hsa03320:PPAR signaling pathway	0.01
	hsa04080:Neuroactive ligand-receptor interaction	0.01
	hsa04024:cAMP signaling pathway	0.03
GO_BP	GO:0006281~DNA repair	0.00
	GO:0016337~single organismal cell-cell adhesion	0.00
	GO:0015671~oxygen transport	0.01
	GO:0043085~positive regulation of catalytic activity	0.01
	GO:0007193~adenylate cyclase-inhibiting G protein coupled receptor signaling pathway	0.01
	GO:0045762~positive regulation of adenylate cyclase activity	0.02
	GO:0000226~microtubule cytoskeleton organization	0.02
	GO:0051899~membrane depolarization	0.04
	GO:0006656~phosphatidylcholine biosynthetic process	0.04
	GO:0019216~regulation of lipid metabolic process	0.04
	GO:0008542~visual learning	0.05
GO_CC	GO:0005887~integral component of plasma membrane	0.01
	GO:0043204~perikaryon	0.04
	GO:0042645~mitochondrial nucleoid	0.04
GO_MF	GO:0015297~antiporter activity	0.00
	GO:0015485~cholesterol binding	0.04

Interaction Analysis

In order to detect cancer development-related genes, a modular network of differentially expressed genes was constructed by weighted gene co-expression network analyses (WGCNA) (Fig. 2), and a total of 322 differentially expressed genes in 5 stable modules, such as black module (21 DEGs), blue module (78 DEGs), brown module (69 DEGs), red module (23 DEGs) and turquoise module (131 DEGs) were screened, as presented in Additional file. The 78 genes in blue module and 23 genes in red module were down-regulated expression in 10 PCOS patients, and up-regulated expression in 13 control samples and 10 PCOS patients treated with pioglitazone, as presented in Fig. 3. The 69 genes in brown module, 21 genes in black module, and 131 genes in turquoise module were up-regulated expression in 10 PCOS patients, and down-regulated expression in 13 control samples and 10 PCOS patients treated with pioglitazone, as presented in Fig. 3.

The correlations of genes of the stable modules in BioGRID 3.4, STRING 10.5, HPRD9 databases were screened, and the interaction network of 104 DEGs was constructed, as presented in Fig. 4. In interaction network, MYC was interacted with ALDH1B1, CDK1, DDX18, EFNB1, FAT1, IPO4, IREB2, SDK1 and TAF12. CDK1 was interacted with AHCTF1, KIF2C, LEO1, MAD1L1, MYC, PTPN6, and REPS2. LNX1 was interacted with MVB12B, NADK, PAFAH1B3, SDK1, ACY3 and USP9X. APOC3 was interacted with APOA2 and APOE. ADCY2 was interacted with GPR18 and HRH2. C3AR1 was interacted with ATP7A, CCL19, PEX16 and SLC7A2. HRH2 was interacted with ADCY2, CALCA and GNGT1. GRIA1 was interacted with CACNG4. MLNR was interacted with GNGT1 and OXT. TAAR2 was interacted with GNGT1. To search for the important genes, the key words (PCOS and pioglitazone), the enriched pathways and the genes that interacted with the drug or that in the interaction network were searched in CTD. A total of 7 important target genes were identified, such as APOC3 was interacted with pioglitazone, ADCY2 involved in cAMP signaling pathway, and the genes (C3AR1, HRH2, GRIA1, MLNR and TAAR2) involved in neuroactive ligand-receptor interaction. In addition, the important target genes were significantly differential expression (Table 2). These results implied that the 7 important target genes were played an important role in the development and progression of PCOS.

Discussion

PCOS is characterised by anovulation, hyperandrogaenemia and insulin resistance. Hyperinsulinaemia is known to be associated with an increase in cardiovascular risk and the development of diabetes mellitus. Insulin-sensitising drugs pioglitazone is a thiazolidinedione drug that can improve the metabolic disorder of PCOS patients [2, 5–7]. Many researchers have reported that the insulin-sensitising drugs pioglitazone could improve the metabolic disorder of PCOS patients, while the mechanisms of development and progression of PCOS remain unclear. In this study, a total of 596 differentially expressed genes were screened, including 379 genes that were up-regulated in case group and down-regulated in control group and treat group, and 217 genes that were down-regulated in case group and up-regulated in control group and treat group. The differentially expressed genes were enriched in PPAR signaling pathway, Neuroactive ligand-receptor interaction, cAMP signaling pathway, of which pathways were involved in the cancer development.

A modular network of differentially expressed genes was constructed by WGCNA, and a total of 322 differentially expressed genes in 5 stable modules, such as black module

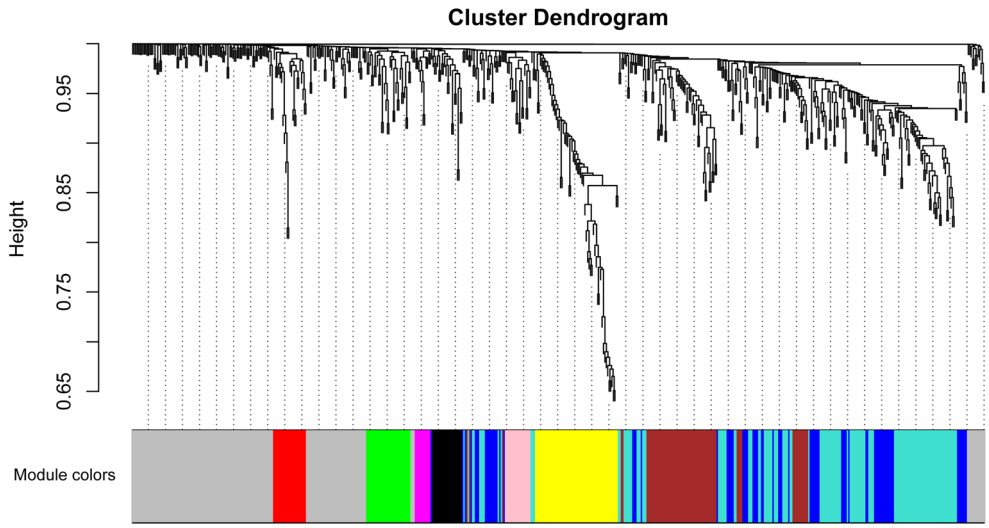

Fig. 2 Weighted gene co-expression network analyses (WGCNA) analysis of the differentially expressed genes. Colours indicate the stable modules

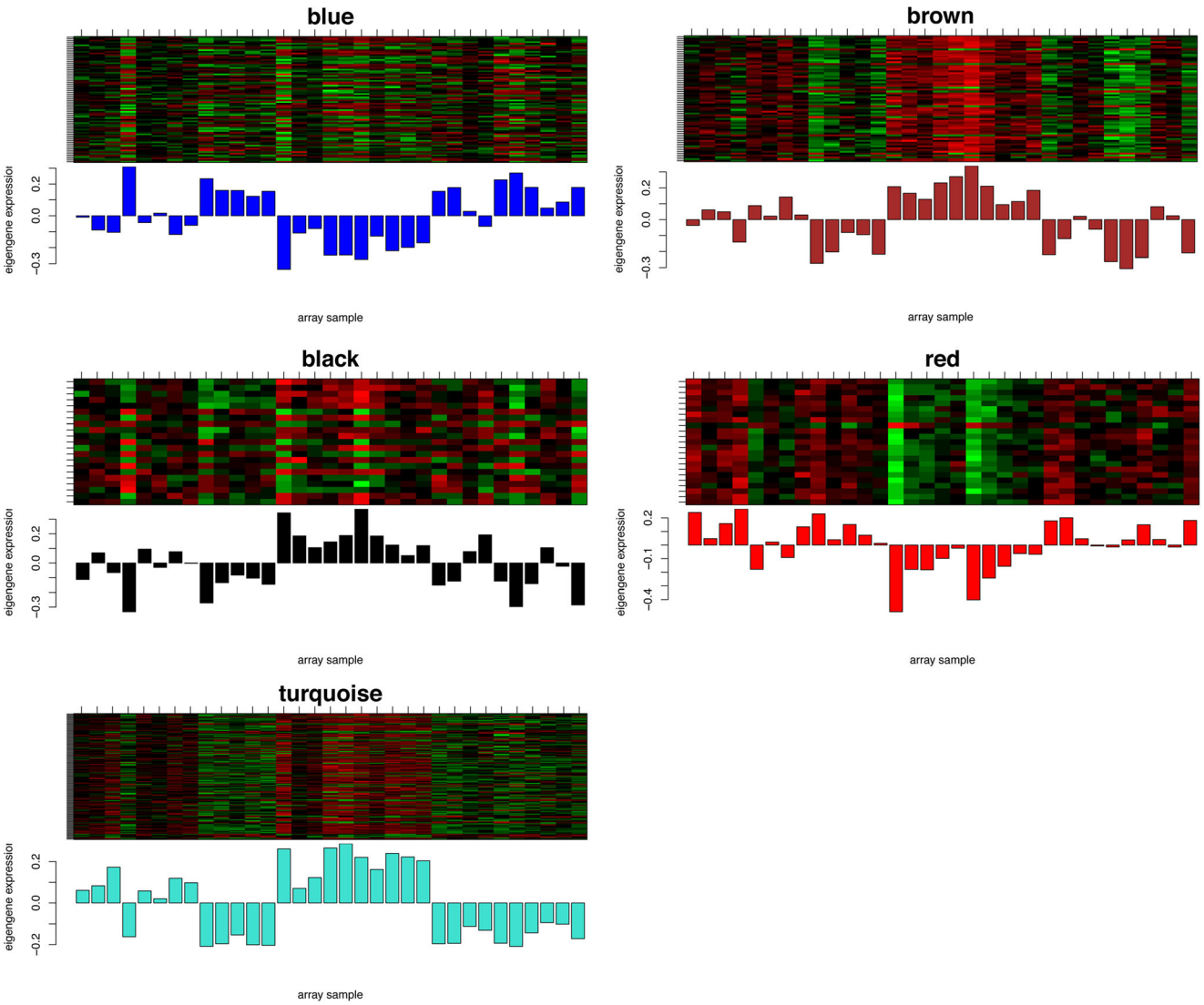

Fig. 3 The expression analysis of 322 differentially expressed genes in 5 stable modules

(21 DEGs), blue module (78 DEGs), brown module (69 DEGs), red module (23 DEGs) and turquoise module (131 DEGs) were screened. The 21 genes in black module, 69 genes in brown module, and 131 genes in turquoise module were up-regulated expression in 10 PCOS patients, and down-regulated expression in 13 control samples and 10 PCOS patients treated with pioglitazone. The 78 genes in blue module and 23 genes in red module were down-regulated expression in 10 PCOS patients, and up-regulated expression in 13 control samples and 10 PCOS patients treated with pioglitazone. The correlations of genes of the stable modules in BioGRID 3.4, STRING 10.5, HPRD9 databases were screened, and the interaction network of 104 DEGs was constructed. In interaction network, MYC was interacted with ALDH1B1, CDK1, DDX18, EFNB1, FAT1, IPO4, IREB2, SDK1 and TAF12. CDK1 was interacted with AHCTF1, KIF2C, LEO1, MAD1L1, MYC, PTPN6, and REPS2. LNX1 was interacted with MVB12B, NADK, PAFAH1B3, SDK1, ACY3 and USP9X. APOC3 was interacted with APOA2 and APOE. ADCY2 was interacted with GPR18 and HRH2. C3AR1 was interacted with ATP7A, CCL19, PEX16 and SLC7A2. HRH2 was interacted with ADCY2, CALCA and GNGT1. GRIA1 was interacted with CACNG4. MLNR was interacted with GNGT1 and OXT. TAAR2 was interacted with GNGT1.

To search for the important genes, the key words (PCOS and pioglitazone), the enriched pathways and the genes that interacted with the drug or that in the interaction network were searched in CTD. A total of 7 important target genes were identified, such as APOC3 was interacted with pioglitazone, ADCY2 involved in cAMP signaling pathway, and the genes (C3AR1, HRH2, GRIA1, MLNR and TAAR2) involved in neuroactive ligand-receptor interaction. These results implied that the 7 important target genes were played an important role in the development and progression of PCOS. The human

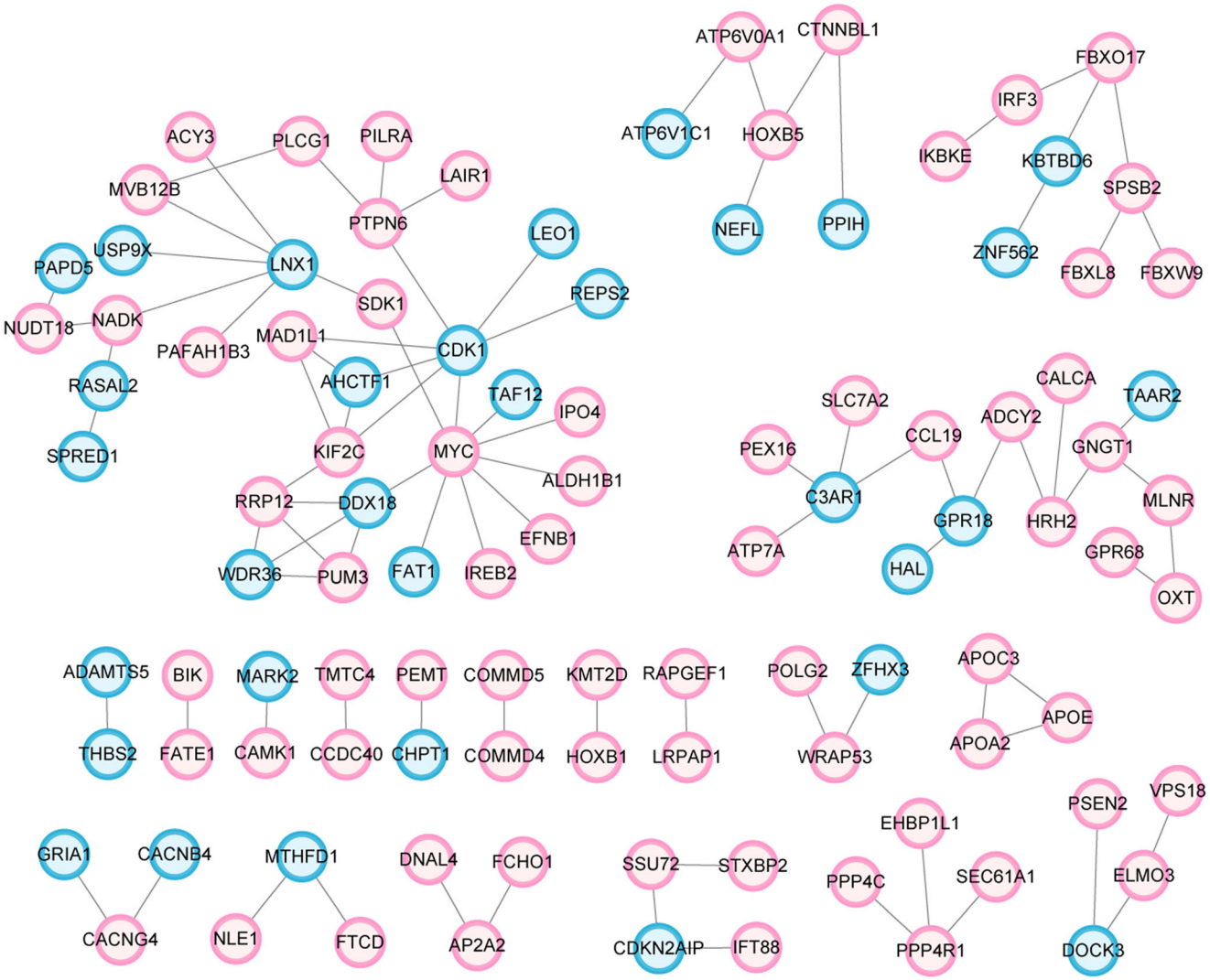

Fig. 4 Interaction network for the differentially expressed genes. Red indicates genes that were up-regulated in case group and down-regulated in control group and treat group, and blue indicates genes that were down-regulated in case group and up-regulated in control group and treat group

apoCs are protein constituents of chylomicrons, VLDL, and HDL and play important roles in the development of hyperlipidemia and atherosclerosis. The apoC family includes apoC-I, apoC-II, and apoC-III [20, 21]. Although all apoCs have roles in lipoprotein metabolism, they have different functions through different pathways. ApoC-II was synthesized with a 22-residue signal peptide [22], and some researchers reported that excess apoC-II on the lipoprotein particle had been demonstrated to inhibit hydrolysis of TGs [23]. Human apoC-III–transgenic mice have impaired clearance of VLDL TG, concomitant with a decreased VLDL apoE to apoC ratio, so they exhibit very elevated levels of VLDL TG [24, 25]. Both apoC-II and apoC-III could inhibit LCAT activity, most likely as a consequence of displacing the activating components of the HDL particle, however, ApoC-I could effectively activate lecithin-cholesterol acyltransferase (LCAT). ApoC-I resides on chylomicrons, VLDLs, and HDLs, and Jong et al. reported that overexpressing apoC-I in homozygous mice had strongly elevated levels of plasma TC and TG due to the inhibitory action of apoC-I on VLDL uptake via hepatic receptors, in particular the low-density lipoprotein receptor–related protein [26–28]. ApoC-I is a constituent of TG-rich lipoproteins, which inhibits hepatic lipase and interferes with lipoprotein clearance by the LDL receptor, the low-density

Table 2 Expression of the important target genes

	LFC_case	P_{fdr}_case	LFC_treat	P_{fdr}_treat
C3AR1	−0.28	2.27E-02	0.34	6.33E-05
HRH2	0.35	3.22E-02	−0.50	1.58E-06
GRIA1	−0.33	3.58E-02	0.53	1.01E-05
MLNR	0.54	4.78E-02	−0.78	5.09E-07
TAAR2	−0.24	2.47E-02	0.39	1.06E-05
ADCY2	0.36	3.58E-02	−0.55	2.91E-07
APOC3	0.42	3.30E-02	−0.80	4.54E-09

lipoprotein receptor–related protein, and the VLDL receptor. Overexpression of apoC-I in transgenic mice produces combined hyperlipidemia along with increased postprandial lipemia [29]. According to the Samanci's report, the results showed that ADC measurement of ovarian stroma was considered as a potential tool for the diagnosis of PCOS [30]. Based on these results, the 7 important target genes (APOC3, ADCY2, C3AR1, HRH2, GRIA1, MLNR and TAAR2) were played an important role in the development and progression of PCOS.

In summary, a modular network of differentially expressed genes was constructed by WGCNA, and a total of 322 differentially expressed genes in 5 stable modules were screened. The correlations of genes of the stable modules in BioGRID 3.4, STRING 10.5, HPRD9 databases were screened, and the interaction network of 104 DEGs was constructed. In addition, some genes and the key words were searched in CTD. Finally, a total of 7 important target genes were identified, such as APOC3 was interacted with pioglitazone, ADCY2 involved in cAMP signaling pathway, and the genes (C3AR1, HRH2, GRIA1, MLNR and TAAR2) involved in neuroactive ligand-receptor interaction. These results implied that the 7 important target genes were played an important role in the development and progression of PCOS.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

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